Changes in Rate of LGI1 Seropositivity During COVID Lockdown

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Introduction

Several reports suggest autoantibody-associated neurological conditions, such as autoimmune encephalitis and myelin-oligodendrocyte glycoprotein (MOG)-antibody associated diseases, may be triggered by the COVID-19 pandemic and associated vaccinations.[1,2] Conversely, public health measures, including lockdowns, might reduce the incidence of immune-mediated neurological disorders through fewer antecedent infective agents.[3] To understand real-world implications of COVID-19-instigated public health measures on the commonest autoantibody-mediated neurological conditions, we compared positivity rates of the most prevalent neuroglial surface autoantibodies between pre-pandemic (2019) and post-pandemic (2020) timepoints. We hypothesised that lockdown measures may reduce the rates of neurological autoantibody positivity.

Methods

Across 2019 and 2020, 42,422 serum samples, excluding repeat samples from individual patients, were routinely tested in Oxford for autoantibodies against the five most requested neuroglial surface antigens: N-methyl-D-aspartate receptor (NMDAR), MOG, aquaporin-4 (AQP4), leucine rich glioma inactivated 1 (LGI1) and contactin associated protein like 2 (CASPR2; **Figure 1A**). We assessed the proportion of positive tests in 90-day epochs, sliding by 15-day intervals, statistically comparing equivalent time windows in 2019 and 2020 (Fisher's exact test with Benjamini-Hochberg multiple-test correction). This study followed STROBE guidelines for case-control studies. A locally approved service evaluation #7694 was granted by Oxford University Hospitals NHS Foundation Trust. Informed consent was not required. Data is available upon reasonable request.

Results

Overall, across the autoantigens, there was a mean of 32.2% decrease in testing (range 23.8%-38.4%; **Figure 1B**) within 90-day windows between 31st March and 15th April in 2020 versus 2019.

Of the five assessed autoantibodies, only the proportion of positive LGI1-antibody results was significantly reduced in the March-June period of 2020 (31st March to 29th June window: false discovery rate=0.002). This period overlapped closely with the first (26th March 2020 to 23rd June 2020) United Kingdom pandemic lockdown (**Figure 1B**).

Discussion

These results suggest a selective reduction in LGI1-antibody positivity rates during the 2020 UK lockdown, by comparison to the same months in 2019. One explanation for these results is a reduction in infectious agent exposure(s) which may trigger this form of autoimmune encephalitis. In NMDAR-antibody encephalitis, a clear link with preceding herpes simplex virus encephalitis is known. Indeed, in NMDAR-antibody encephalitis and in MOG antibody diseases, prodromal infectious symptoms are common.[4] Yet, such direct or indirect infectious associations are rarely recognised in LGI1-antibody encephalitis, although a modest seasonal association has been reported once.[5]

Limitations of this analysis include the absence of clinical data (including time of symptom onset) from the patients with autoantibodies and that paired CSF testing was not requested alongside >90% of sera. However, this analysis compares data across autoantibodies, thereby reducing the risk of onset time biases, and it was our aim to examine serum positivity in diseases where the autoimmunisation is likely to begin peripherally.[6] Further, testing biases may have resulted from altered patient/clinician behaviours during the COVID-19 pandemic, despite data comparisons across different autoantibodies. This may be especially true for patients with LGI1-antibodies where older

patients may be more prone to complete self-isolation or show greater reluctance to attend healthcare services, and limited (seizure-dominant) presentations may not immediately prompt medical appointments. Other potential limitations include not studying the vaccine rollout period and not directly studying seasonality by normalising across sequential years: these can be addressed in future studies.

Overall, our data suggest that LGI1-antibody production may be incited by one or several organism(s), potentially including SARS-CoV2, and that future public health measures may selectively influence the incidence of this encephalitis. These data have implications for affected patients and ongoing multinational clinical trials seeking to recruit these patients.

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Figure legend

Figure 1. Autoantibody positivity rates across 2019 versus 2020. A. Autoantibody testing requests (grey) and positive results (red) for the 5 commonest neurological cell-surface autoantibodies. **B.** The maximum relative reduction in testing rates between sliding 90-day windows in 2019 and 2020 for each autoantibody. **C.** Scatter plot comparing proportional test positivity in 2019 compared to 2020, using sliding 90-day windows. Negative $\log_2$ enrichment values indicate lower proportional positivity in 2020 relative to 2019. The size of points is proportional to the $-\log_{10}$ p-value of each comparison. Lines connect adjacent points for each autoantibody.